REMARKS

Claims 1-6 and 8-23 are pending. Applicant has amended claim 23 to further clarify the claimed invention. Support for this amendment may be found in the specification at least at page 4, line 16 to page 6, line 32. Applicant thanks the Examiner for the telephone conference of June 21, 2005.

The Office maintains its rejection of claims 1-6 and 8-22 under 35 U.S.C. § 103 and now rejects claim 23 under this section and under 35 U.S.C. § 112, second paragraph. Applicant addresses each rejection below.

Rejection Under 35 U.S.C. §112

Claim 23 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. According to the Office, the term "simulating *in vivo* interactions" is indefinite because it is unclear what conditions are being simulated and unclear how the recited method steps achieve the goal of simulating *in vivo* interactions. Office Action at page 2.

Regarding the Office's query as to what conditions are simulated, Applicant refers to the preamble of claim 23 which recites "simulating *in vivo* interactions between the IgE antibody, the IgE antibody's ligand and the IgE antibody's receptor." As discussed below, the method steps themselves simulate these interactions.

In vivo, IgE antibodies and the ligands they encounter are free to interact with each other in solution. The antibody or the ligand are not naturally immobilized to a stationary surface. The invention of claim 23 uses a "free dissolved ligand" as recited in step (a) and a liquid sample in which the IgE to be detected and/or quantified moves freely in solution, allowing complexes that comprise the IgE antibody and the ligand to form prior to contact with the IgE receptor. Thus, these natural *in vivo* interactions

between ligands and antibodies are simulated. Moreover, *in vivo*, the IgE receptors CD23 (FcεRII) and FcεRI are associated with cells. These cells, such as activated B cells and T cells (CD23) or mast cells and basophils (FcεRI) are free to circulate throughout the body. They are not normally immobilized to one location. The use of an IgE receptor bound to a carrier simulates this antibody/receptor interaction, the carrier acting as an artificial cell to which the receptor is bound. See also the specification at pages 5 and 6.

Moreover, the assay confers the ability to detect and/or quantify the amount of IgE that can bind to its natural receptor rather than simply quantifying the total level of IgE present in the sample. For example, quantifying the amount of IgE that binds to FcεRI in turn quantifies the amount of physiologically active IgE available to bind to mast cells and potentially stimulate an inflammatory or allergic reaction to the ligand.

In sum, the method steps claim 23 by virtue of their characteristics, simulate *in vivo* conditions. To facilitate prosecution, however, Applicant has amended claim 23 to describe what was already implicit in the claim as discussed above. Applicant believes that this amendment further clarifies the relationship between the method steps of claim 23 and the simulation of *in vivo* conditions.

Applicant requests that the Office withdraw its rejection of claim 23.

Rejections Under 35 U.S.C. §103

The Office maintains its rejection of claims 1-5, 8-14, 16, 21, and 22 under 35 U.S.C. § 103(a) as allegedly obvious over Johansen (U.S. Pat. 6,087,188) in view of Johnson (U.S. Pat. 6,034,066) and Frank 2 (U.S. Pat. 6,060,326). Applicant notes that claim 23 has now been added to this rejection. The Office continues to assert that

Johansen teaches a method of detecting an antibody using a ligand bound to biotin; an antibody to the antibody to be detected; a chemiluminescent acridinium compound bound to avidin; and a method for quantifying specific antibodies. Office Action at page 3. The Office acknowledges that Johansen does not teach using an IgE receptor to detect or quantify IgE. *Id.* at page 5. Regarding Johnson, the Office alleges that this reference teaches the role of CD23 in regulating the immune response, such as IgE responses. *Id.* The Office believes that Frank 2 teaches a method for detecting IgE antibodies using a human Fc epsilon receptor. *Id.* The Office combines these references, suggesting that it would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson and Frank 2 to measure IgE according to the method of Johansen. *Id.* at pages 5 and 6. In addition, with regard to claim 16, the Office believes it would have been obvious to use enough ligand molecules to optimize binding of all the IgE molecules in a sample. *Id.*

In the previous Office Action, the Office asserted that, because claims 1-6 and 8-22 allegedly do not recite the concept of simulating *in vivo* conditions, Applicant's argument that the invention simulates any interference from other immunoglobulins or other potentially interfering components in a sample, was not relevant. Office Action of September 8, 2004, at page 7. Thus, Applicant introduced claim 23 in its last response, which included the language provided to the Examiner during an in-person interview on November 19, 2004. Claim 23 recites the concept of simulating *in vivo* conditions. The Office now responds by noting that it has not given the concept of stimulating *in vivo* conditions, as described in the claim's preamble, "patentable weight." Office Action at page 6. Applicant respectfully traverses.

As Applicant explained above regarding the rejection of claim 23 under 35 U.S.C. § 112, second paragraph, the concept of simulating *in vivo* conditions is not just in the preamble of claim 23, but also implicit in the steps of claim 23. Applicant thanks the Examiner for the telephone conference of June 21, 2005, and her clarification that for this concept to be considered, it should be present not only in the preamble of claim 23, but also in the body of claim 23. And Applicant has amended claim 23 to describe this relationship. Specifically, the use of a "free dissolved ligand," the use of a liquid sample containing the IgE to be detected and/or quantified, and the use of an IgE receptor bound to a carrier simulates interactions that occur *in vivo*. These features are also evident in claims 1-6 and 8-22. Thus, the invention does not merely detect all IgE in a sample. By mimicking the interaction of IgE antibodies with their antigens and their receptors, the invention detects only the IgE available for eliciting an allergic response. As Applicant has noted, none of the three references cited by the Office teach the importance of mimicking *in vivo* interactions between antibody and antigen or antibody and receptor.

Moreover, the fact that Johansen does not teach the use of IgE receptors in their assay method is not insignificant. The invention's use of IgE receptors provides a level of information beyond that provided by assays that merely detect the presence of IgE antibodies using, for example, anti-IgE antibodies. IgE receptors have certain biological functions by virtue of their presence on different cells types of the body. As explained above, activated B cells and T cells express CD23 while mast cells and basophils express FcεRI on their surfaces. So, for example, when using FcεRI in the assays of the invention, the skilled artisan can determine the quantity of antigen-specific IgE

antibodies in a sample that will bind to FcεRI and thus bind to FcεRI on mast cells and basophils. This information in turn gives the skilled artisan insight into the propensity for mast cells and basophils in the patient from which the sample was taken to activate and participate in inflammatory responses associated with allergic reactions. In sum, the skilled artisan can elucidate the patient's immune status with regard to IgE function on an antigen-specific level.

Johnson simply discusses the functions of CD23 in the immune system. This reference does not suggest the use of CD23 in any method for detecting or quantifying IgE, let alone a method that does so while mimicking the *in vivo* interaction of IgE with its target antigen. Thus, Johnson does not provide any motivation to use CD23 in the method of Johansen and, conversely, Johansen does not provide the requisite motivation to use IgE receptors. Knowing this, the Office looks to Frank 2 for the motivation to combine and a reasonable expectation of success in doing so.

In the previous Office Action, the Office cited Frank 2 at column 5, lines 47-56 and asserted that this citation allegedly shows that Frank 2's assays use the same components as Johansen. Office Action of September 8, 2004, at pages 8 and 9. Applicant explained that this citation from Frank 2 discussed a formulation which uses at least an IgE receptor and may or may not use other reagents like antibodies that bind to different portions of an IgE molecule. In contrast, Johansen used anti-IgE antibodies to detect IgE. Thus, Johansen and Frank 2 do not use the same set of reagents.[1]

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[1] The Office seems to implicitly agree with Applicant's position that Frank 2 does not use the same reagents as Johansen. Specifically, the Office states that "if Frank 2 teaches the same method and reagents as in Johansen, then Frank 2 would be applied to a 102 rejection instead of a 103 rejection." Office Action at page 9. In light of this statement, the fact that the Office applies Frank 2 in a 103

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The Office now responds by again citing Frank 2 at column 5, lines 47-56 and citing column 2, lines 11-17 and column 8, lines 50-56. Office Action at page 8. Neither of these new citations provides the requisite motivation to combine these references as the Office suggests.

The first new citation apparently indicates that the invention of Frank 2 "relates to the discovery of purified, high affinity canine Fc epsilon receptor[s] [that] . . . can be used in canine epsilon immunoglobulin (referred to herein as . . . IgE antibody) - based detection methods and kits." Column 2, lines 11-17. Applicant notes that this citation refers to canine receptors, not to human receptors as the Office has repeatedly suggested. See, e.g., Office Action at page 9, lines 16 and 17. A general suggestion that an IgE receptor might be used in the genus of detection assays does not suggest its use in a particular species of detection assay, such as the assay of the instant invention. In addition, as noted above, the instant invention does not merely detect IgE antibodies, it does so while mimicking *in vivo* interactions.

The second new citation provides that "a complex can be detected in a variety of ways including . . . a particulate-based assay (e.g., using particulates such as . . . magnetic particles or plastic polymers . . .)." Column 8, lines 50-56. The Office's citation of Frank 2 does not teach in what capacity such particulates would be used in the assay. And, *arguendo*, even if Frank 2 did suggest using a particulate in combination with a receptor, it would not necessarily motivate the skilled artisan to use it in the assay of Johansen. Two references that may use similar components do not

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rejection implies that the Office believes that Frank 2 uses different reagents and methods from those of Johansen.

necessarily use them in the same way and therefore do imply that such components can be used interchangeably.

Finally, Applicant respectfully notes that the Office has not yet explained why the skilled artisan would have a reasonable expectation of success in combining the teaching of Johansen, Frank 2, and Johnson. Rather, the Office now asserts that Applicant has not pointed to any factors that would prevent the combined references from having a reasonable expectation of success. The Office improperly places the initial burden of proof on Applicant. Rather, the Office must initially prove a prima facie case of obviousness based on a motivation to combine and a reasonable expectation of success. As Applicant has explained in this and previous responses, the Office has not met this burden. For the above reasons, Applicant requests that the Office withdraw its rejection of claims 1-5, 8-14, 16, and 21-23 under 35 U.S.C. § 103(a) as allegedly obvious over Johansen, Johnson, and Frank 2.

Claims 6 and 17-20 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Johansen and in further view of Frank 2 and Arnold (U.S. Patent 6,004,745). According to the Office, it would have been obvious to one of ordinary skilled in the art to add the label molecule after a first separation step and then separating the non-complexed labels as discussed in Arnold using the reagents in the method of Johansen as modified by Frank 2. Office Action at pages 6 and 7.

As Applicant previously noted, Arnold does not cure the lack of motivation or the lack of a reasonable expectation of success as discussed above. The Office has still not addressed Arnold's shortfall because it believes that it has provided the requisite motivation to combine via its discussion of Johansen and Frank 2 and therefore need

not look to Arnold for such motivation. The Office further alleges that Arnold teaches two separation steps, the first to remove antigen that has not bound to immobilized antibodies and the second separation step to remove any labeled, non-immobilized antibodies that have not bound to the antigen.

Arnold's method does not use an IgE receptor or mention the use of an IgE receptor. Rather, Arnold uses two antibodies, one immobilized to a surface and the other labeled. The Office has not explained why the skilled artisan would replace *only* the immobilized antibody with an IgE receptor to arrive at the invention instead of replacing both antibodies, which, as alleged by the Office, may provide more specificity and sensitivity to the method. There is no teaching or suggestion anywhere in the cited references that such a single replacement would offer any particular advantage over a double replacement. Moreover, the Office has not explained why one would be motivated to use two separation steps, as allegedly taught by Arnold, in the method of Johansen *and* to further modify this combination by using the formulations described by Frank 2. Finally, Arnold, like Johansen and Frank 2, does not teach an assay that mimics in vivo interactions between an antigen and IgE and between IgE and its receptor. For the reasons set forth above, claims 6 and 17-20 are not obvious in view of Johansen, Frank 2, and Arnold. Applicant requests that this rejection be withdrawn.

Conclusion

Applicant respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing pending claims 1-6 and 8-23 in condition for allowance. Applicant submits that the proposed amendment of claim 23 does not raise new issues or necessitate the undertaking of any additional search of the art by the

Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Furthermore, Applicant submits that the entry of this Amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Finally, Applicant requests the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: July 6, 2005

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